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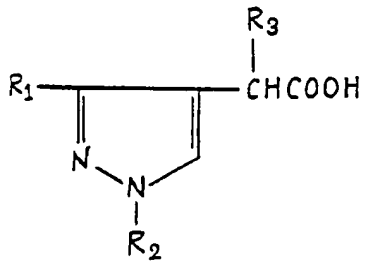
(71) Applicant: **SANWA KAGAKU KENKYUSHO CO., LTD.**
No. 35, Higashi-sotobori-cho
Higashi-ku Nagoya-shi Aichi-ken(JP)

(72) Inventor: **Sawai, Kiichi c/o Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)
Inventor: **Kurono, Masayasu Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)
Inventor: **Mitani, Takahiko Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)
Inventor: **Niu, Kazumi Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)
Inventor: **Asano, Kyoichi Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)

(74) Representative: **Wächtershäuser, Günter, Dr.**
Tal 29
D-8000 München 2(DE)

(54) Use of pyrazole derivatives in the treatment of immunity diseases and nephropathy.

(57) A pharmaceutical composition comprising as an effective ingredient, a pyrazole compound of the formula



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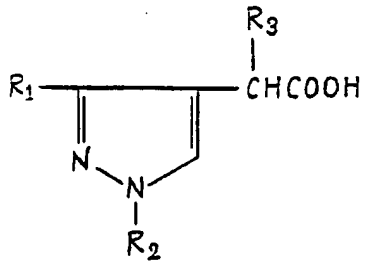
wherein each of R_1 and R_2 is phenyl or p-halogenophenyl radical, respectively, and R_3 is hydrogen atom or methyl radical, or a salt thereof. The composition is used for curing immunity diseases and a nephropathy.

Pharmaceutical composition

The present invention relates to a pharmaceutical composition and more particularly to that for medical treating immunity diseases and a nephropathy.

It has been known that pyrazole compounds represented by the following formula, and more particularly 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid (generally called as --Lonazolac--) has pharmaceutical activities of antiinflammatory, antipyretic action and sedative action and shows a relatively low toxicity (BP 1373212 and USP 4146721).



wherein each of R_1 and R_2 is phenyl or p-halogenophenyl radical, respectively, and R_3 is hydrogen atom or methyl radical.

Further, it has been reported that the pyrazole compounds of said Formula and other than said specified compound also show antiinflammatory ["Rinsyo Meneki" (may be translated as --Clinical Immunity--) Vol. 18, page 387 (1986)].

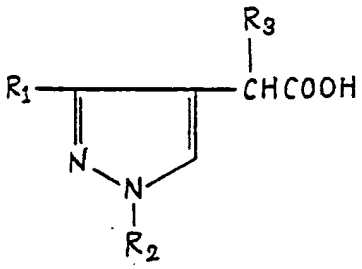
While, as an ingredient for curing a nephropathy, a diuretic drug has generally been employed. It is required for attaining the purpose, however, to give the drug over a relatively long period of time. As a result, the drug may show a toxicity due to its accumulation or an intercurrent disease is apt to be ocurred. Therefore, it has eargerly been required for a more safety drug for curing the nephropathy.

An action of antiinflammatic agents to immunity system has been noted with great interest, in connection with prostaglandin. In view of this view point, the pyrazole compounds shown by said Formula are effective for curing immuno-acceleratory diseases but give a bad effect to immuno-inhibitory diseases and thus so considered that this type medicine should not be dosed to the patient with the latter immunity disease.

The present inventors have, however, found through their careful study and investigation that the immuno-inhibitory action ofthe compounds shown by the Formula, which has been commonly considered from the antiinflammatory action thereof is not correct but, in actual, the compounds show an immunity controlling or regulating action.

Therefore, one of the objects of the invention lies in use the compound(s) shown by the Formula, as an immunity controlling ingredient to cure various immunity diseases.

According to the invention, the object can be attained by an immunity control composition comprising an effective amount of a pyrazole compound of the formula



wherein each of R_1 and R_2 is phenyl or p-halogenophenyl radical, respectively, and R_3 is hydrogen atom or methyl radical, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

In view of the immunity controlling action of the compounds, the inventors have further studied and

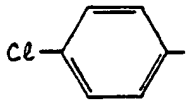
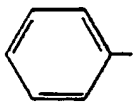
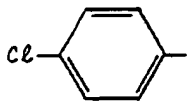
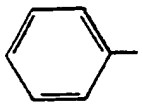
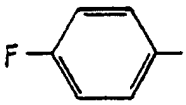
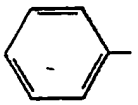
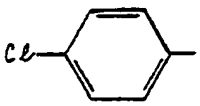
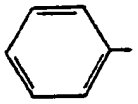
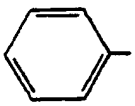
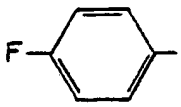
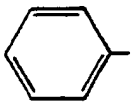
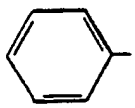
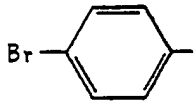
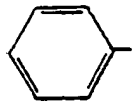
investigated to utilize the compounds as an drug for medical treating the nephropathy and finally found that it is effective therefor, especially to glomerulitis, chromic nephritis and nephrose.

Therefore, another object of the invention is to provide a composition for medical treating the nephropathy, which does not show or shows a relatively low toxicity and causes almost no intercurrent disease due to its side effect, even it it will be administrated over a long period of time.

According to the invention, this object can be attained by a pharmaceutical composition for medical treating nephropaty, which comprises an effective amount of the pyrazole compound shown by said formula, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

Among the compounds reprsented by said Formula, exemplar one to be employed as the effective ingredient for the pharmaceutical composition according to the invention may be shown in following Table 1.

Table 1

Comp.	R_1	R_2	R_3	Salt	m.p.
1			H	-	150 (℃)
2			H	Ca	270
3			H	-	150
4			$-CH_3$	-	180
5			H	-	126
6			H	-	275
7			H	-	141

Each of the compounds shown by said Formula shows, in general, a low solubility to water, ether or the like usual solvent and thus, when the compound is made into a medicine, the pharmaceutically acceptable carrier can be employed for improving its solubility and to stabilize the same. As the carrier, natural high molecular substances, for instance, gelatin, chitin, chitocine, aliphatic acid esters thereof and the like; synthetic high molecular substances, for instance, cellulosic, vinylic, acrylic, glycolic and the like synthetic polymers; succharoids, for instance, lactose, starch, cellurose, cyclic dextrin or the like; and any mixture of

these substances may be listed.

For preparing the medicine, a filler, binder, disintegrator or the like additive may be composed, in addition to the carrier, but such additive should, of course, be selected from those having no physico-chemical reaction with the compound shown by said Formula, as the main ingredient and established as inactive in a retarded immuno-reactive test from the pharmacological view point.

The compound and/or salt thereof can be made into the medicine without any special limitation. A formulation for the medicine is carried out in a conventional manner to form a tablet, capsule, granule, powder or the like solid one, injection, solution for oral administration, embrocation or the like liquid one, ointment, jelly or the like semi-solid one. A dosing amount of the compound or salt for human depends on a kind of same, a symptom of the patient, form of the medicine and other factors but, in general, is selected in a range of 10 to 1500mg/day for an adult. In case of oral dosage, however, about 150mg/day is preferably for the adult.

The invention will now be further explained with reference to Examples for preparing a pharmaceutical composition or medicine according to the invention and Pharmacological Test Examples which will refer to drawings, in which

Fig. 1 is a graph showing results that a compound as effective ingredient for the composition according to the invention was administrated in various amounts to mice sensitized with antigen of 2×10^8 SRBC to check an antibody production ability, with an index of number of PFC in their spleen cells;

Fig. 2 is a graph showing results similar to Fig. 1, excepting that the mice were sensitized with the antigen of 2×10^7 SRBC;

Figs. 3A, 3B and 3C are graphs showing an influence of the compound upon a juvenilizing reaction in spleen cells caused by mitogen of ConA, PHA and LPS, which were indicated with stimulation index by amount of ^{3}H-thymine;

Fig. 4 is a graph showing results that an influence of the compound upon an adjuvant arthritis in rats was checked with an inhibition of swelling;

Fig. 5 is a graph showing results that the compound was administrated to self-immuno diseased mic to check an amount of urine protein with their positive ratio;

Fig. 6 is a graph showing results that the compound and other drugs was administrated to the self-immuno diseased mice to check an amount of urea nitrogen; and

Fig. 7 is a graph showing results that the compound was administrated to the self-immuno diseased mice to check a ratio of spleen weight to the body weight.

Please note that the compound employed for the Examples was --Compound 2--in said Table 1, namely calcium salt of 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid (hereinafter referred to as --Compound 2--).

Example 1 (Injection)

To 0.1% aqueous solution of saccaroaliphatic acid ester, the Compound 2 and mannitol were added to make a concentration thereof in 1.5% and 2%, respectively and then the mixture was stirred to dissolve the substances. The resulting solution was filtered for debacterization, charged into vials by each 2ml and freeze dried to seal the same.

This dry powder accommodated in the vial can be dissolved in a physical saline, when it should be injected to a patient.

Example 2 (Embrocation)

To 0.2% aqueous solution of saccharoaliphatic acid ester, the Compound 2 was added to make its concentration in 0.2% and the mixture was stirred to dissolve the compound and to obtain a desired embrocation.

This embrocation can directly be applied on skin or mucosa.

Example 3 (Ointment)

To 0.5% aqu ous solution of saccharoaliphatic acid ester, the Compound 2 was added to make its concentration in 0.2% and the mixture was stirred to dissolve the compound. The resulting solution was spray-dried to obtain a powd ry composition. The composition and other ingredients were composed under the following prescription to prepare a desired ointment, in a conventional manner.

Ingredient	Amounts (g)
Said composition	0.5
Diethyl sebacinate	8.0
Spermaceti	5.0
Sodium phosphate of polyoxyethyleneoilether	6.0
Sodium benzoate	0.5
Vaseline	remainder
Total	100.0 (g)

Example 4 (Suppository)

The powdery composition obtained by the way of the procedure in Example 3 was dispersed in a molten higher fatty acid glyceride under the following prescription to prepare a desired suppository, in a conventional manner.

Ingredient	Amount (mg)
Said composition	60
Fatty base (Cacao fat)	1640
	1700 mg/piece

Example 5 (Tablet)

The compound 2 and hydroxypropylcellulose were mixed in weight ratio of 1 : 3 and the mixture was milled to obtain a powdery composition. The composition and other ingredient were composed under the following prescription and treated in a conventional manner to prepare desired tablets.

Ingredient	Amount (mg)
Said composition	100
Lactose	85
Carboxymethylcellulose (Ca salt)	7
Silicic anhydride	1
Magnesium stearate	7
	200 mg/tablet

Example 6 (Capsule)

The powdery composition obtained by the way of the procedure in Example 5 and other ingredients were composed under the following prescription and treated and filled in a gelatin capsule, in a conventional manner to prepare a desired preparation.

Ingredient	Amount (mg)
Said composition	100
Lactose	97
Hydroxypropylcellulose	2
Magnesium stearate	1
	200 mg/capsule

Parmacological Test Example 1(Actual use of ointment)

The ointment obtained by the procedure of Example 3 was given to each of volunteers (20 persons) who have a rubefaction due to a bite or hemorrhoid, or a monopathy due to ascariasis or the like, to use the ointment freely.

Thereafter, an opinionaire research was made to obtain results as shown in following Table 2. As seen from the Table, all most all of the persons have reported that the ointment imroves the condition.

Table 2

Item	Persons		
	Improved	Doubtful	Ingravescense
Rubefaction	18	1	1
Ascariasis	16	3	1

Pharmacological Test Example 2 (Influence on productivity of antibody)

a) Object

An influence of the Compound 2 on productivity of an antibody is checked by sensitizing normal mice with an antigen in an amount for developing an immuno-response to its maximum level due to sufficient stimulation by the antigen, or in another amount which causes no sufficient proceeding of immuno-response due to insufficient stimulation by the antigen, and then administrating the compound.

b) Operation

Each group of BALB/c mice was sensitized by injecting from tail vein a sheep erythrocyte (SRBC, 2 x 10^8 or 2 x 10^7 pieces), as the antigen. While, the Compound 2 suspended in 5% gum arabic solution was orally administrated to the mice in an amount of 0.1, 1, 10 or 100mg/kg in twice of just after the sensitization and the next day thereof.

On the 4th day after the sensitization, the spleen was enucleated and number of PFC in spleen cells was determined to make the number as an index for ability on antibody production.

c) Result and consideration

Results in both systems sensitized with SRBC 2 x 10^8 pieces and 2 x 10^7 pieces are shown in Figs. 1 and 2, respectively. As seen from the Figures, there are such tendencies that the PFC is decreased in th former system but in the latter system, the PFC is increased.

It is apparent from the results that the Compound 2 develops the immunity controlling action.

Pharmacological Test Example 3 (Influence on juvenilization of lymphocyte)

a) Object

An effect of the Compound 2 to juvenilization of spleen cells in nomal mice, which is to be caused by an action of mitogen is checked.

b) Operation

To a culture medium (RPMZ 1640 medium containing 10% FCS) containing the Compound 2 in 0.01 to 100 mg/ml, a suspension of spleen cells (5 x 10^5/ml) on BALB/c female mouse was added, and then ConA, PHA or LPS as the mitogen was added. Thereafter, an amount of ^{3}H-thymine taken into the spleen cells was determined to check the effect of the Compound 2 from the amount as an index therefor.

c) Results and consideration

Results are shown in Figs. 3A, 3B and 3C with a relation between a stimulation index and concentration of the Compound 2. It can be seen from the Figures that the Compound 2 apparently accelerate the juvenilization of lymphocytes, due to ConA or PHA but remains only showing a tendency of acceleration, on that due to LPS.

This fact show that the influence of the Compound 2 on immunity system develops through T-cells.

Pharmacological Test Example 4 (Action to adjuvant arthritis of rat)

a) Object

An effect of the Compound 2 on prevention of adjuvant arthritis is checked.

b) Operation

An adjuvant (prepared by suspending 0.6mg of killed mycobacterium o butiricum in 0.05ml of fluid paraffin) was injected to SD female rats through calx skin of a hind leg to cause an arthritis. On each day after 1, 3, 5, 7, 14, 21 and 28 days from the adjuvant administration, a volume of the leg was measured to determine a ratio of edema (swelling). Moreover, an inflammation degree at the not treated hind leg, both

front legs, ear and tail was measured on 14th, 21st and 28th day from the administration to evaluate by an index (score designation).

As to the group giving the tested drugs inclusive of the Compound 2, the drug was orally administrated once a day by a predetermined amount over 28 days inclusive of that the adjuvant was injected.

c) Results and consideration

The results on inhibition of swelling and inflammation score are shown in Fig. 4 and following Table 3, respectively.

From Fig. 4, it can be seen that an effect of inhibition on the secondary inflammation develops on the groups, to which the Compound 2 was given at 3 or 10mg/kg. This inhibition effect is reflected to the results of the inflammation scores in Table 3 and an incidence of the swelling, which is shown in a parenthesis on the Table.

It is believed that a fact that the Compound 2 inhibits not the primary but secondary swelling supports its immunity controlling action suggested from the results shown in the Test Examples 2 and 3.

TABLE 3

Compound	Dose (mg/kg/day, p.o.)	Inflammation Score		
		14th day	21st day	28th day
No (control)	-	2.9 ± 0.8 (7/9)	5.3 ± 1.1 (8/9)	5.0 ± 1.0 (8/9)
Compound 2	1	5.0 ± 0.9 (9/10)	5.6 ± 1.2 (8/10)	4.8 ± 1.1 (8/10)
ditto	3	3.2 ± 1.0 (6/10)	3.7 ± 1.2 (6/10)	2.7 ± 1.0 (5/10)
ditto	10	3.7 ± 1.0 (7/10)	5.5 ± 1.2 (9/10)	7.0 ± 1.3 (8/10)
ditto	30	3.8 ± 1.1 (7/10)	5.7 ± 1.4 (7/10)	6.0 ± 1.6 (7/10)
Indomethacin	1	2.0 ± 0.9 (4/10)	2.4 ± 1.3 (3/10)	2.2 ± 1.1 (4/10)
Diclofenac Na	3	4.2 ± 1.1 (7/10)	4.3 ± 1.2 (7/10)	5.6 ± 1.3 (10/10)
Robenzarit	25	3.6 ± 1.3 (5/10)	4.7 ± 1.3 (7/10)	5.4 ± 1.5 (7/10)

Pharmacological Test Example 5 (Action to generation of self-immuno disease)

a) Object

An action of the Compound 2 for preventing from generation of self-immuno nephritis in MRL/1 mice is checked.

b) Operation

To MRL/1 female mice (age of 6 weeks), the Compound 2 was orally administrated once a day in an amount of 1, 3, 10 or 30mg/kg/day over 12 weeks. Within the testing period, a urin protein was measured once a week to check a positive ratio in each week, by determining as --positive animal--who shows the urine protein concentration of more than 100mg/dl. Further, a urea nitrogen in blood was measured at the next day from the final administration to evaluate the action of the tested drugs inclusive of the Compound 2 from serum biochemistrical view point and to check an influence on weight increase of the spleen.

c) Results and consideration

Results on the positive ratio on urine protein and the urea nitrogen in blood are shown in Figs. 5 and 6, respectively. From the Figures, it can beseen that the compound 2 inhibits the generation of nephritis and a preferable amount therefor is 3mg/kg/day.

While, results on ratio of spleen weight to body weight are shown in Fig. 7. From the Figure, it can be considered that the Compound 2 has a tendency for decreasing the ratio and a preferable amount therefor is 3mg/kg/day.

Further, results of phatological analysis and an evaluation thereof are given in following Table 4.

TABLE 4

Item	Control	Compound A				Indomethacin
		1mg/kg	3mg/kg	10mg/kg	30mg/kg	1mg/kg
Number of animals	10	10	10	10	10	10
No. of observed glomerulus	100	100	100	100	100	100
Glomerulosclerosis	1	0	0	0	0	1
Glomerulocapsular nephritis						
Heavy	13	7	1	2	4	4
Medium	43	25	22	27	30	52
Light	42	56	66	68	54	42
Normal	1	12	11	3	12	1
Analysis of variance		**	***	**	**	

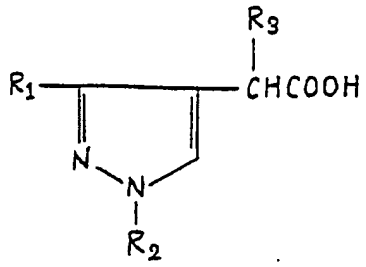
Significance Difference :

*p < 0.05, **p < 0.01, ***p < 0.001

In general non-steroid type anti-inflammation drugs, the actions as seen on the Compound 2 can not be recognized and thus results as shown in Figs. 5 to 7 support a fact that the compound 2 has the immunity controlling action suggested by the results of the Pharmacological Test Examples 2 and 3, together with the results of the Pharmacological Test Example 4.

Claims

1. An immunity control composition comprising an effective amount of a pyrazole compound of the formula

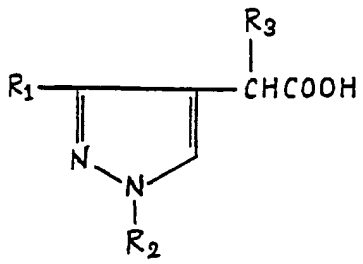


wherein each of R_1 and R_2 is phenyl or p-halogenophenyl radical, respectively, and R_3 is hydrogen atom or methyl radical, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

2. An immunity control composition as claimed in Claim 1, wherein said pyrazole compound is select d from the group consisting of 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid and pharmaceutically acceptable salts thereof.

3. An immunity control composition as claimed in Claim 2, wherein said pyrazole compound is 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid, calcium salt.

4. A composition for medical treating a nephropathy, which comprises an effective amount of a pyrazol compound of the formula



wherein each of R_1 and R_2 is phenyl or p-halogenophenyl radical, respectively, and R_3 is hydrogen atom or methyl radical, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

5. A composition as claimed in Claim 4, wherein said pyrazole compound is selected from the group consisting of 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid and pharmaceutically acceptable salts thereof.

6. A composition as claimed in Claim 5, wherein said pyrazole compound is 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid, calcium salt.

FIG. 1

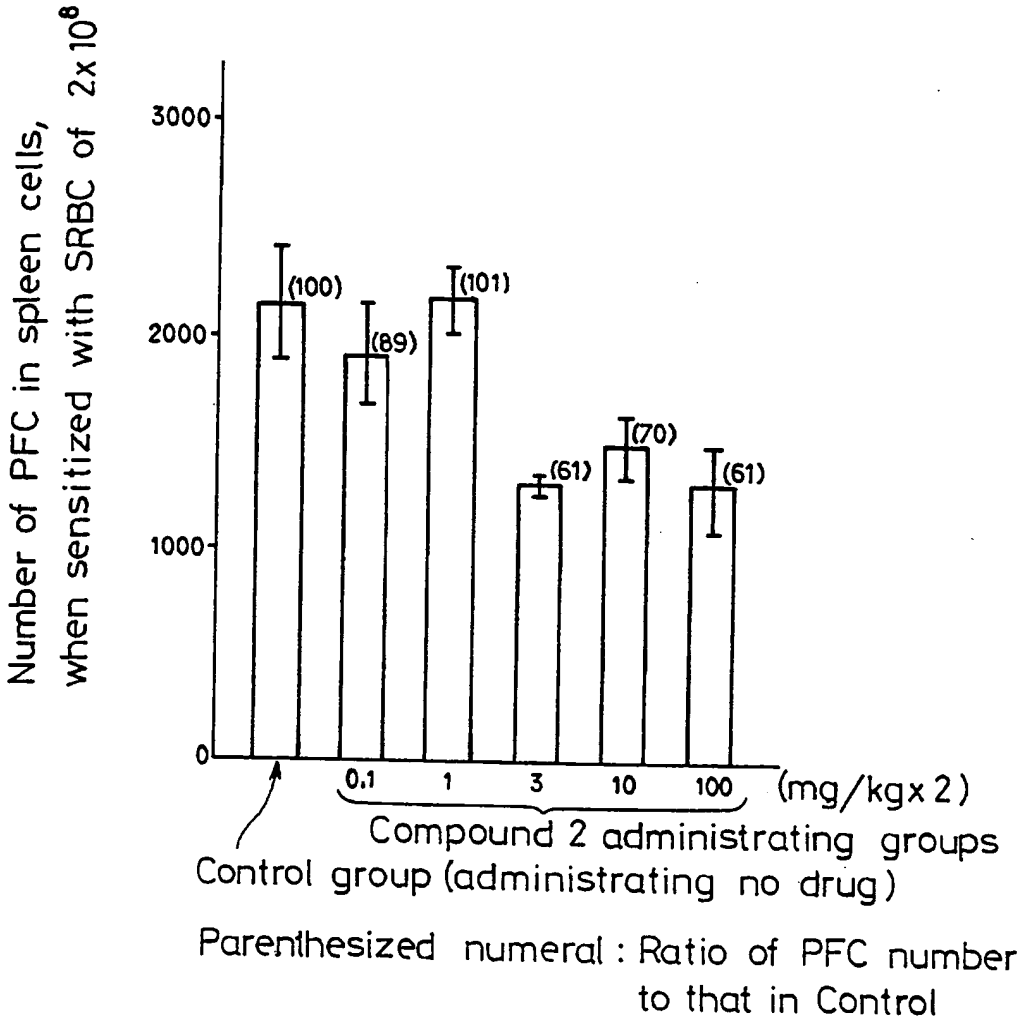

Number of PFC in spleen cells, when sensitized with SRBC of 2×10^8
3000
2000
1000
0
(100)
(89)
(101)
(61)
(70)
(61)
0.1
1
3
10
100
(mg/kg x 2)
Compound 2 administrating groups
Control group (administrating no drug)
Parenthesized numeral : Ratio of PFC number to that in Control

FIG. 2

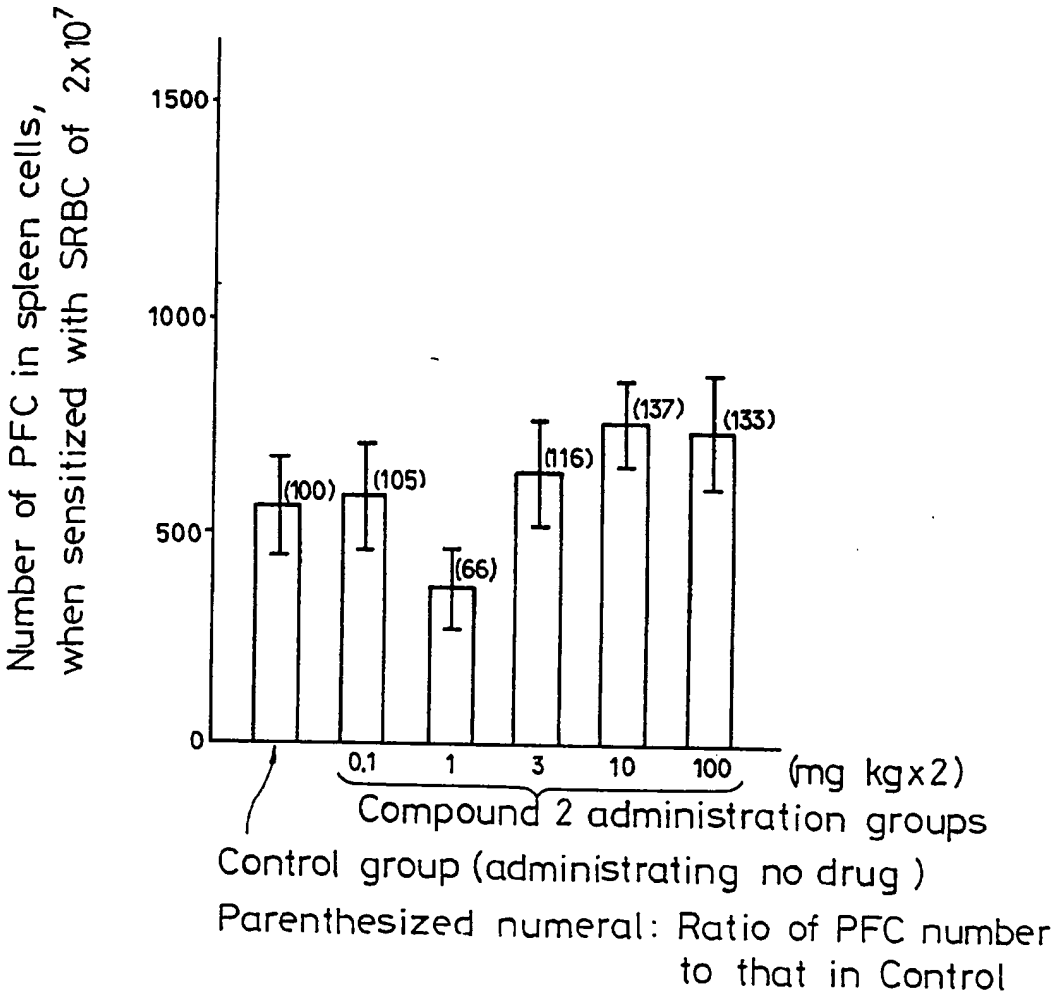
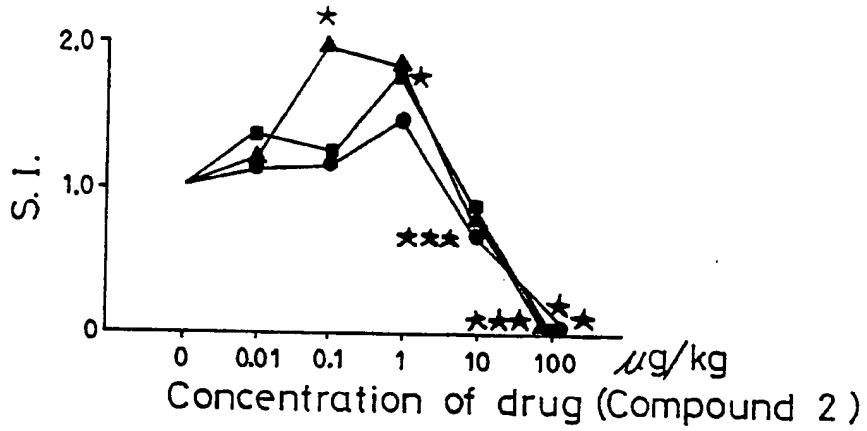

Number of PFC in spleen cells, when sensitized with SRBC of 2×10^7
1500
1000
500
0
(100)
(105)
(66)
(116)
(137)
(133)
0.1
1
3
10
100
(mg kg×2)
Compound 2 administration groups
Control group (administrating no drug)
Parenthesized numeral: Ratio of PFC number to that in Control

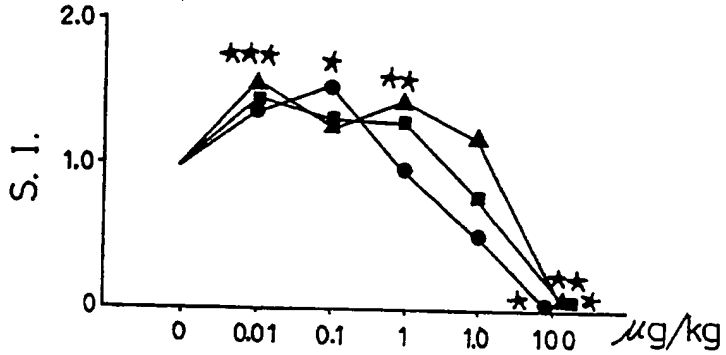
FIG. 3A



Con A
- ▲ 0.25 μg/ml
- ■ 0.5 μg/ml
- ● 1.0 μg/ml

Significance difference
- ★ P < 0.05
- ★★ P < 0.01
- ★★★ P < 0.001

FIG. 3B



PHA
- ▲ 5 μg/ml
- ■ 10 μg/ml
- ● 20 μg/ml

Significance difference
- ★ P < 0.05
- ★★ P < 0.01
- ★★★ P < 0.001

FIG. 3C

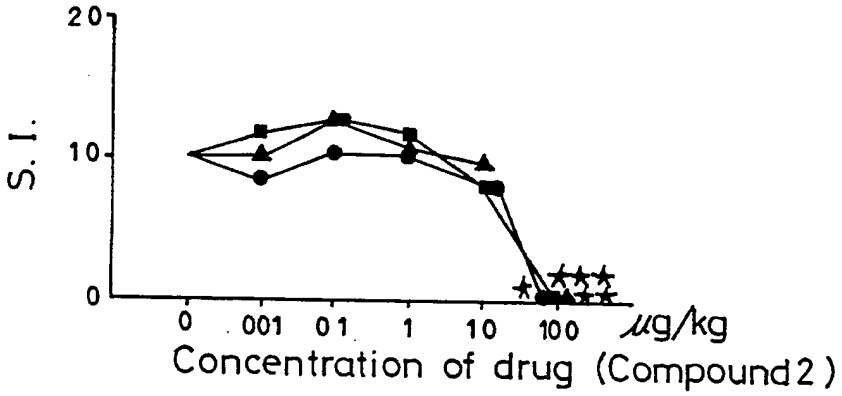
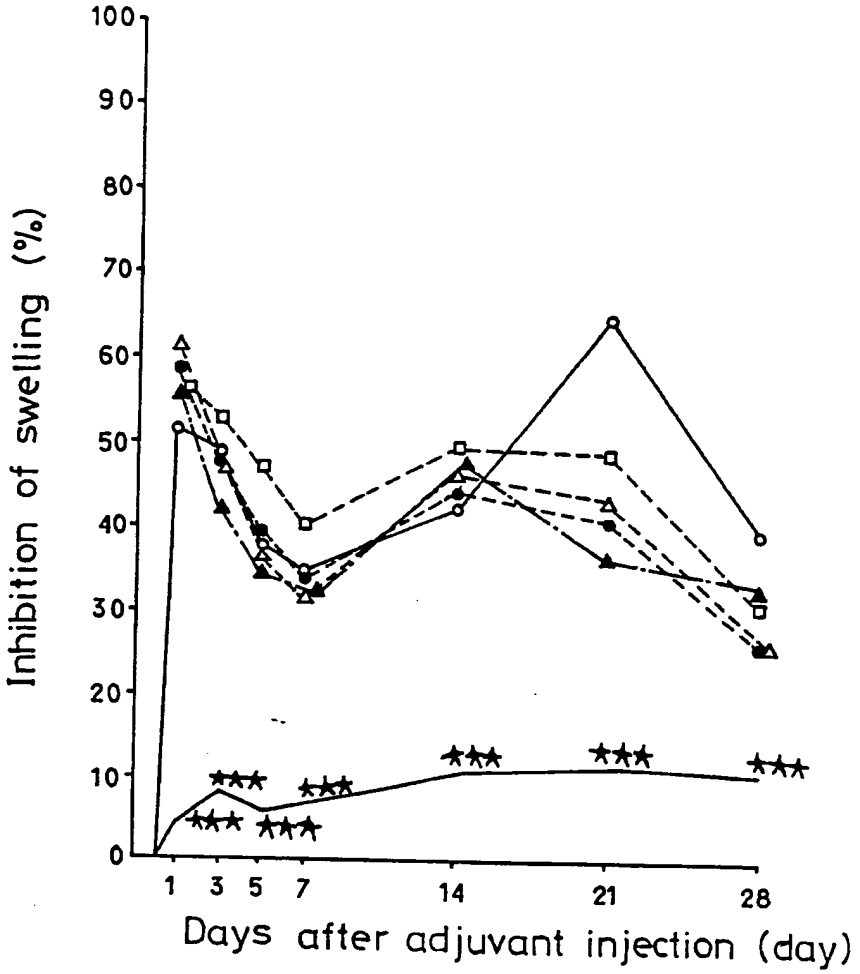

20
10
0
S. I.
0
001
01
1
10
100
μg/kg
Concentration of drug (Compound 2)
LPS
▲ 5 μg/kg
■ 10 μg/kg
● 20 μg/kg
Significance difference
★ P < 0.05
★★ P < 0.01
★★★ P < 0.001

FIG. 4



○——○ : Control
●----● : Drug (Compound 2) administration, 1 (mg kg day)
△----△ : Ditto, 3
▲—·—▲ : Ditto, 10
□----□ : Ditto, 30
——— : None treatment
★★★ : Sinificance difference ($p < 0.001$)

FIG. 5

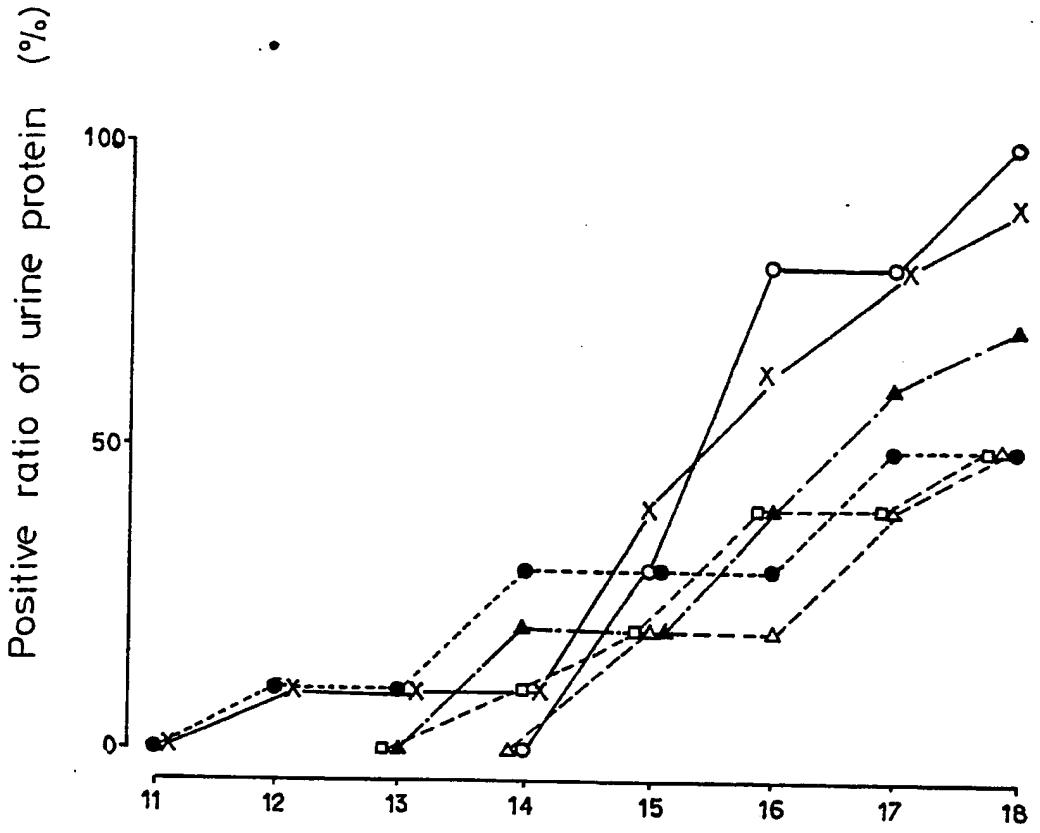
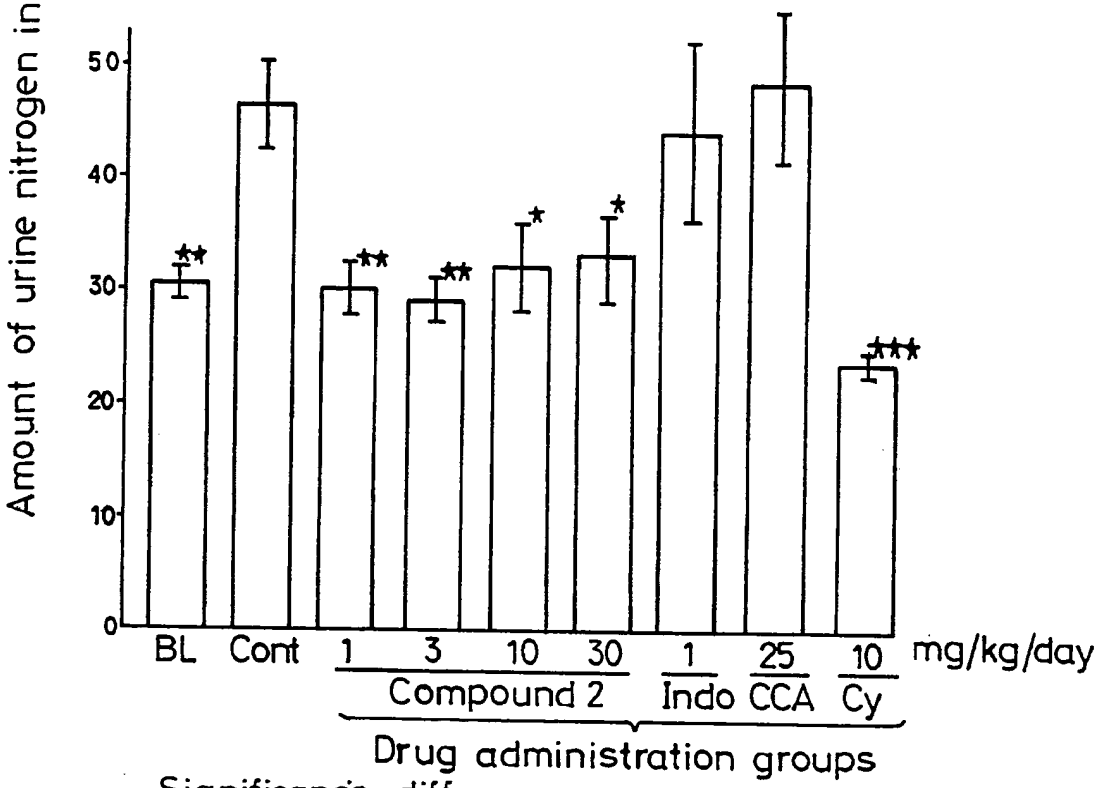

Positive ratio of urine protein (%)
100
50
0
11
12
13
14
15
16
17
18
Weeks from first administration of drug (week)
: Control
: Drug (Compound 2) administration, 1 (mg/kg/day)
: Ditto, 3
: Ditto, 10
: Ditto, 30
: Drug (Indomethacin) administration, 1

FIG. 6



Significance difference:

★ : $p < 0.05$

★★ : $p < 0.01$

★★★ : $p < 0.001$

BL : C57BL mice (6 heads)

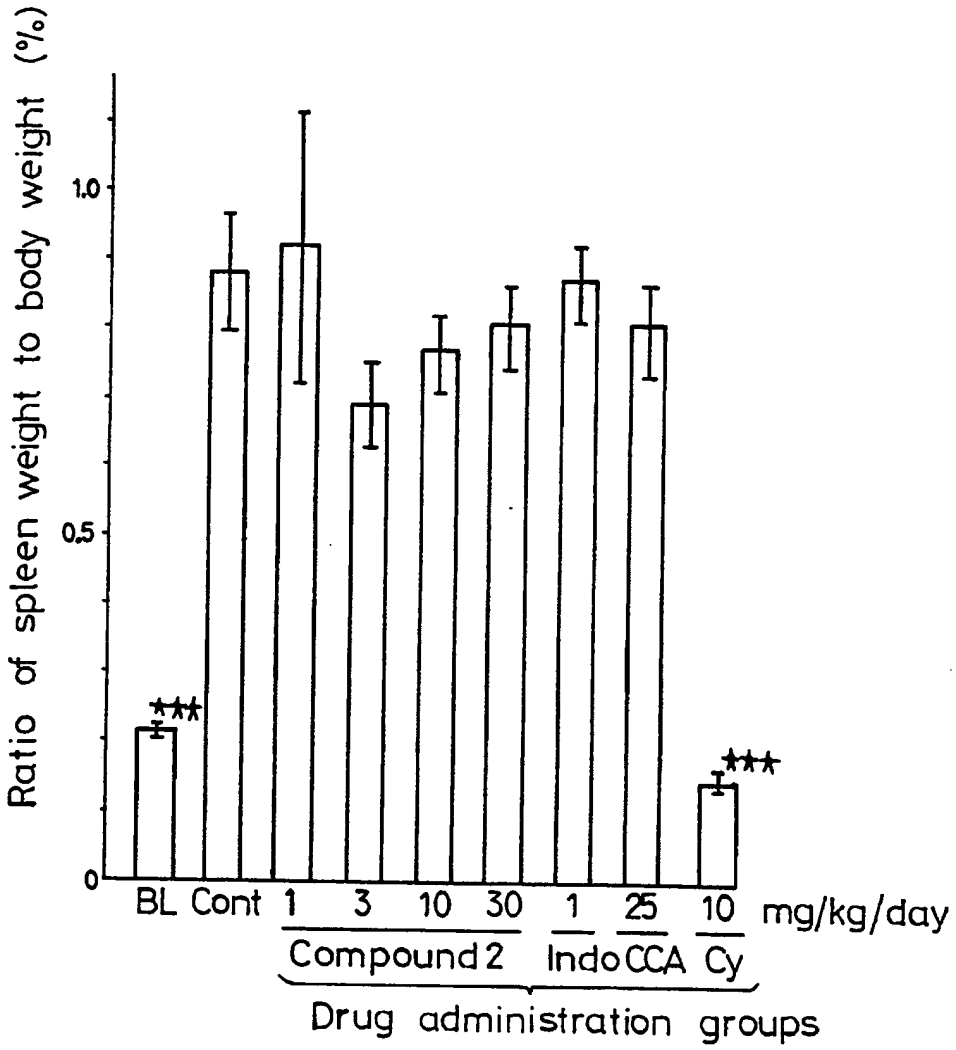
Cont : Control (administrating no drug)

Indo : Indomethacin

CCA : Robenzarit

Cy : Cycrophostamide

FIG. 7



Significance difference : ★★★ ($p < 0.001$)

BL : C57BL mice (6 heads)
Cont : Control (administrating no drug)
Indo : Indomethacin
CCA : Robenzarit
Cy : Cycrophostamide

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Office européen des brevets

(11) Publication number: **0 272 704**
A3

(12) # EUROPEAN PATENT APPLICATION

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05.03.87 JP 51030/87

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(71) Applicant: **SANWA KAGAKU KENKYUSHO CO., LTD.**
No. 35, Higashi-sotobori-cho
Higashi-ku Nagoya-shi Aichi-ken(JP)

(72) Inventor: **Sawai, Kiichi c/o Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)

Inventor: **Kurono, Masayasu Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)

Inventor: **Mitani, Takahiko Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)

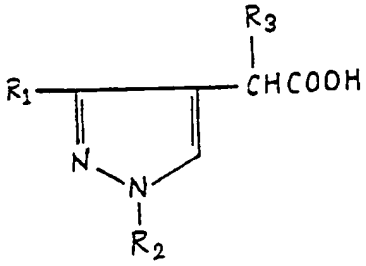
Inventor: **Niu, Kazumi Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)

Inventor: **Asano, Kyoichi Sanwa Kagaku Kenkyusho Co., Ltd.**
35, Higashi-sotobori-cho Higashi-ku
Nagoya-shi Aichi-ken(JP)

(74) Representative: **Wächtershäuser, Günter, Dr.**
Tal 29
D-8000 München 2(DE)

(54) **Use of pyrazole derivatives in the treatment of immunity diseases and nephropathy.**

(57) A pharmaceutical composition comprising as an effective ingredient, a pyrazole compound of the formula



wherein each of R_1 and R_2 is phenyl or p-halogenophenyl radical, respectively, and R_3 is hydrogen atom or methyl radical, or a salt thereof. The composition is used for curing immunity diseases and a nephropathy.

EP 0 272 704 A3

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 87 11 9256

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	INT. J. TISS REAC., vol. 7, no. 4, 1985, pages 263-265, Bioscience Ediprint Inc. R. GÖRTZ et al.: "Blocking of mononuclear cell activation by lonazolac" * Whole article *	1-6	A 61 K 31/415
A	MED. MONATSSCHR. PHARM., vol. 6, no. 12, 1983, pages 354-355; C. WERNING: "Chronische Polyarthristis" * Whole article *	1-6	
A	THERAPIEWOCHE, vol. 34, no. 4, 1985, G. Braun, Verlag Zeitschriften, Karsruhe, DE H. Chr. BENÖHR: "Medikamentöse ./.		TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely:

Claims searched incompletely: 1-6

Claims not searched:

Reason for the limitation of the search:

The term "immunity control" is not sufficiently descriptivr for a disease. Claims 1-6 have been searched as though the claims had been drafted in the corrcet form: "use of the compound in the manufacture of a medicament for the treatment if immunological disorders"

Place of search	Date of completion of the search	Examiner
The Hague	31-07-1990	GOETZ

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

See sheet -B-

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims:

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	Behandlung der chronischen Polyarthritis" * Abstract; table 3 *	1-6	
	--		
A	THERAPIEWOCHE, vol. 31, 1981, pages 5895-5901, Verlag G. Braun, Karlsruhe, DE I. ABELE et al.: "Ergebnisse einer Feldstudie mit Lonazolac-Ca (Irritren), einem neuen nichtsteroidalen Antiphlogistikum/ Antirheumatikum" * Whole article *	4-6	TECHNICAL FIELDS SEARCHED (Int Cl 4)
	--		
A	ZEITSCHRIFT FÜR RHEUMATOLOGIE, vol. 40, 1981, pages 161-164 G. LONAUER et al.: "Lonazolac-Ca - ein nicht steroidales Antirheumatikum. Klinische Langzeitstudie bei chronischer Polyarthritis" * Whole article *	4-6	

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1-3 (completely), 4-6 (partially): Use of the compound in the manufacture of a medicament for the treatment of immunological disorders.
2. Claims 4-6 (partially): Use of the compound in the manufacture of a medicament for the treatment of a nephropathy not involved by immunological processes.

N.B.:
If the applicant wants subject 2 to be searched he is invited to take EPC Articles 83 and 84 and EPC Rule 45 into consideration.